Dermatology Dilemmas: Interesting Dermatology Cases: Urticaria
November 13, 2010

Sarbjit S. Saini, M.D.

Johns Hopkins University

Disclosure Slide

- Research Interests-Genentech, NIH
- Other Interests-Consultant to Genentech, Pharmacyclics, Medimmune, Array, Kendle

Learning Objectives

At the conclusion of this session, participants should be able to:

- Discuss unusual chronic urticaria cases
- Discuss distinguishing features that are helpful in diagnosis of urticaria
- Identify the elements to urticaria work-up
- Examine controversies in approach to the disease

Competencies: PC,MK,PBL

Non-FDA approved use for all drugs

Differential Diagnosis for Chronic Urticaria

I. Acute urticaria/angioedema

A. Drug, Food Insect hypersensitivity

B. Idiopathic

C. Pseudoallergic reactions: Radiocontrast dye

D. Toxic reaction

E. Contact urticaria

F. Immune complex:Serum sickness, Post-viral

II.Chronic urticaria/angioedema

A. "Autoimmune" or Idiopathic

B. Physical: Dermographism, Cholinergic, Delayed pressure, Solar, Cold, Vibratory, Aquagenic

C. Presumed immune complex: Urticarial vasculitis,Collagen vascular disease associated

D. Hypersensitivity reactions: Drug or Food allergy

III. Rare syndromes: Urticaria pigmentosa/systemic mastocytosis

Diagnostic Approach to CU

Thorough History and Physical Exam

- Duration of episodes and lesions appearance (photos)
- Medication/food history
- Identify physical triggers (~20%)
- Consider infections

Possible Lab studies

- Basic series: CBC, BMP, LFTs, Urinalysis
- Other testing guided by physical exam or history
- Extended: WESR, anti-thyroid antibodies,TSH,C3,C4
- “Autoimmune” tests- ASST, Basophil CD203c or CIU index?
- Skin biopsy to exclude vasculitis or define cellular picture in atypical cases: prolonged lesion duration, pigment changes, epithelial changes

Current CIU Therapies

Symptoms

Mild

Severe

- Avoid ASA
- Antihistamines- control itch, reduce episodes
  - H1-blockers: non-sedating, older generation
  - H2-blockers
  - Tricyclics-doxepin

+ Leukotriene antagonists

+ Oral corticosteroids tapers

+ Consider Immunomodulators
  - Sulfasalazine, cyclosporine, dapsone, colchicine, omalizumab

- Severe patients on multiple drug classes

CIU Patients who fail Anti-Histamines

- Consider a skin biopsy to define histology
  - **Lymphocyte predominant urticaria**
  - **Neutrophil predominant urticaria**
- Exclude other skin disorders
  - Vasculitis- lesions > 3 days,
    - Purpura, pigmentation
    - Burning or painful lesions
    - Immune complex associated disease
  - Mastocytosis-check serum tryptase, otherr systemic signs

Options for neutrophil-rich urticaria

- Dapsone: 25 to 100 mg daily
  - Baseline CBC, liver, renal, UA, G-6-PD deficiency
  - Follow CBC, LFTs weekly then monthly
  - SE: Anemia, peripheral neuropathy, GI distress, methemoglobenemia
  - Case series:
    - Acta Derm Venereol 2005;85(3):254-5
    - J of Dermatological Treatment 2008; 19;92-96
    - JEADV 2008;22: 481-486
- Colchicine: 500 mg daily to 3x/day
  - SE: GI distress, baseline labs
- Both used in hypocomplementemic vasculitis

Options for lymphocyte eosinophil-rich CIU

- Sulfasalazine: 500 mg to 4 gms daily
- 19 severe CIU patients (Arch Dermatol. 2006;142)
  - 14 had significant improvement, 7 had SE
  - 13 able to stop systemic steroids
  - SE: HA, GI distress, cytopenias, rarely cyanosis, reversible oligospermia, hepatotoxicity
  - Requires blood monitoring (CBC, LFTs)
- Cyclosporine (2-5 mg/Kg), Hydroxychloroquine
- Evidence-based review,Morgan and Khan Annals 2008

Cases for discussion

- CIU recalcitrant to anti-histamines
- CIU failing cyclosporine
- CIU with neutrophilia on biopsy
- Progressive CIU with systemic findings

CASE I: History

47 yo male endocrinologist

- 5 mos of hives and swelling
- **Each hive lasts < 24 hrs, no bruising**
- Irbesartan (Avapro) & atorvastatin (Lipitor) stopped without change
- Initiated prednisone 40 mg + fexofenadine 180 mg
- Tried ranitidine, montelukast, hydroxyzine
- Unable to wean < 15 mg of prednisone x 4 mo
- Tried 20 mg doxepin without change

Case I: Past History

- Atopic: AR and sinusitis, rash to ibuprofen (Motrin)
  - Pos skin test to DM, grass, tree, ragweed
- PMH: Type I DM, hypothyroidism
- Meds: Insulin, levothyroxine, fluticasone (Flonase), pred 15 mg, hydroxyzine 100 mg tid, doxepin 20 mg bid, montelukast (Singulair) 10 mg qd, ranitidine 150 mg bid

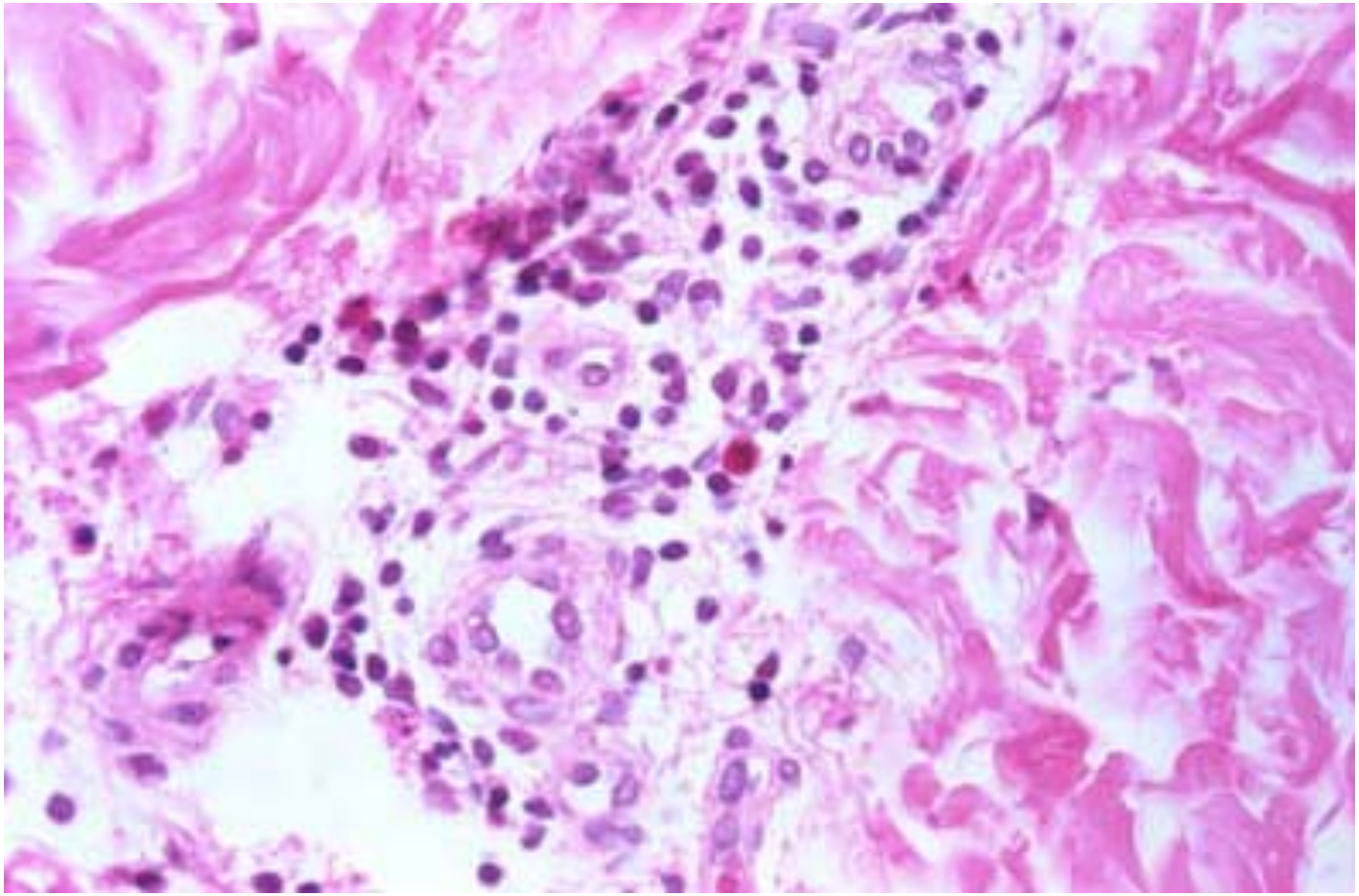
Physical exam and Labs

- Skin with scattered hives, neg dermographism
- Remainder of exam WNL
- Recent labs- NL C1 esterase, NL C3, C4; Neg ANA; WESR 1, Neg H. Pylori, Neg stool for O and P

Impression and Recommendations

- Severe CIU
  - Recalcitrant to anti-histamines/ LTRA
  - Failure to wean < 15 mg/d prednisone
  - Euthyroid by history and labs
- Options
  - #1 Increase of doxepin to 50 mg
  - #2 Trial of synthroid (TSH 4.7, +/- TPO Ab)
  - #3 **Skin biopsy (off prednisone x 7 d)**
    - Characterize lesions, exclude vasculitis
    - Use of immunomodulator: Sulfasalazine/dapsone ?
    - Obtain baseline labs

Biopsy of Skin Lesion



No leukocytoclasia, fibrin deposition, endothelial swelling

Laboratory Studies

- Skin biopsy: Neg DIF, perivascular and interstitial infiltrate of lymphocytes and eosinophils: *classic urticaria*
- Baseline labs
  - CBC- elevated WBC (on prednisone)
  - CMP, TFT all repeated and WNL

Clinical course-I

- Weaned off pred on increased doxepin
  - extremely fatigued, poor function/QOL
- Increase of levothyroxine (Synthroid) led to no change
- Agreed to begin sulfasalazine
  - 500 mg to 2 gm/day in weekly 500 mg steps
  - Weekly labs okay (CBC, AST, ALT)
- At 2 gm/day for 1 wk
  - no benefit, maybe worse?
  - 5 day prednisone course (on beach vacation)

Clinical course-II

- 6 wks of Sulfa: Much improved
  - Off hydroxyzine, down to doxepin 20 mg
  - fexofenodine (Allegra)/ montelukast (Singulair) continued for AR/hives
- 2 mos: Can I reduce Sulfa? Off doxepin
- 4 mos: Sulfa to 1500 mg/d + montelukast (Singulair)
- 5 mos: Sulfa to 1000 mg/d
- 6 mos: Sulfa to 500 mg/d x 1mo then off
  - asked to restart on H1 blocker to allow sulfa taper
- 9 mos: skin sx's on fexofenodine (Allegra)/ montelukast (Singulair)
  - restart sulfa, full dose in 1mo with response
  - Tapered more slowly, 3 month intervals

Clinical Case II- History

61 yo male with daily, pruritic hives x 4 mos

- last 3 hrs-48 hrs; **no pain or skin changes**
- H/o angioedema, 1 ER visit
- Stopped all meds, no sx change
- Fexofenadine (Allegra), cetirizine (Zyrtec), montelukast (Singulair), ranitidine (Zantac) failed
- Responds to oral steroids (has DM)
- CsA 300 mg/d helped, but had inc BP
- CsA 200 mg/d still with inc BP
- Dapsone 100 mg/d for 1 month failed
- Retried CsA 150 mg/d + doxepin 50 mg

Case II- Past History

- Labs: CBC, CMP, H. pylori, TSH, ANA all WNL, food RASTs negative
- PMH: Diabetes, Hypercholesterolemia
- Meds: CSA 150 mg/d, ranitidine (Zantac) 150 mg bid, fexofenadine (Allegra) 180 mg, montelukast (Singulair) 10 mg, cetirizine (Zyrtec) 10 mg, Atorvastatin (Lipitor) 40 mg
- PE: **BP 170/90**; repeat **157/92**
- Skin: diffuse urticaria on trunk

Case II- Impression and Recommendations

- Severe CIU refractory to standard meds
  - Responds to steroids and 300 mg CsA (4mg/kg/d)
  - Hypertensive on 150 mg/d of CsA
  - Failed multiple anti-histamines
- Recommendations
  - Stop CsA due to BP issues
  - Updosing of doxepin
  - Skin biopsy and repeat labs studies when off CsA

Case II- Biopsy and follow-up

- Skin biopsy: superficial dermatitis with eosinophils, rare neutrophils
- Follow-up
  - Off CsA: repeat BP 156/78
  - Doxepin helped only for a few weeks
  - Labs: CBC, CMP, UA all fine
  - Began sulfasalazine after SE discussion
  - Weekly dose escalation and labs checks

Case II: Follow-up on Sulfa

- 1 month on sulfa-worse?, 5 d of Pred
- 6 wk on sulfa, improved sx's, **BP 128/76**
  - drop in doxepin 50 to 40 mg with hives
  - slow doxepin taper
- 2 mos: doing well, labs ok, on multiple meds
- 3 mos: no sx's, restarted ASA, metformin
- 4-7 mos: weaned off LTRA, cetirizine (Zyrtec), doxepin, maintain fexofenadine (Allegra) and sulfasalazine; labs ok
- 9 mos: drop sulfa to 1500 mg/d, labs ok
- 14 mos: Sulfa to 500 mg/bid,labs ok
- 18 mos: Off sulfa, on fexofenadine (Allegra) only
- 24 mos: off H1 blocker, remains sx-free

Take home points

- Skin bx is helpful in anti-histamine resistant cases and severe cases
  - Define infiltrate and exclude vasculitis
- Onset of sulfasalazine effect is slow !
  - Set patient expectations
  - Monitor labs weekly, monthly, quarterly
  - Maintain an antihistamine during sulfa tapers
- Trials of immunomodulators may be needed
- Stepwise wean of multiple meds in a class (H1 blockers)

Case III- History

- 27 yo female 6 yr of hives
  - **Lesions with "burning" symptom**
- Failed with H1, H2, doxepin 50 mg
  - OD'd on doxepin, discontinued
  - Tried hydroxychloroquine (Plaquenil) but failed
  - Pred 50 mg with taper for 3 mos
  - Skin biopsy (off pred) dermal infiltrate with **neutrophil predominance**, no vasculitis seen
  - Labs: CBC, LFTs, C3, C4,C1q, Renal, UA all WNL

Case III- Past History

- Atopic: Childhood asthma
- Ills: Depression
- ROS: 40# wt gain, joint pains with hives
- Meds: sertraline (Zoloft), ranitidine (Zantac) 150 mg bid, pred 10 mg, cetirizine (Zyrtec) 10 mg
- PE: few urticaria on wrist, flushes easily

Case III-Impression and Recommendations

- Severe CIU
  - Antihistamine refractory
  - Prednisone dependent
  - Neutrophil-predominant urticaria
- Options
  - Trial of dapsone- SE of infections, leukopenia,GI distress, anemia
  - 25 mg with weekly 25 mg increase to 100 mg
  - Weekly checks of CBC, LFTs

Case III-Clinical Course

- 4 wks of dapsone 50 mg: triggers of hives are reduced, pred tapered
- Increased to 75 mg and labs checked in 1 wk
  - Hgb/Hct 11/36 drops to 10/30; off pred
  - Repeat Hct/ Hgb stable, kept on 75 mg
- 3 mos of dapsone: off pred x 2 mos, on cetirizine (Zyrtec) 10 and doing well, no sx's
- Repeat labs q mos x 3 then q 3 mos
- Plan dapsone taper as tolerated, weaned

Case IV-History (1)

- 79 yo Caucasian male with 2 yr history of daily hives
- 2005- Pruritic rash, lesion < 24 hrs; no residual skin changes
  - No clear triggers
  - Treated with benadryl with minimal relief
- Cough post URI sxs, no change with Abx
  - Cough waxed and waned, D/C of ACEI and AR2B
  - Spirometry nml
  - Dxed with GERD and started on omeprazole

Case IV: History (2)

- **Rash progresses** involve almost entire body surface (face, palms, soles relatively spared)
- Skin biopsy in 1/06: perivascular infiltrate of predominantly mononuclear cells
- 6/06: cetirizine, fexofenadine, montelukast
  - No benefit and stopped all after 1 month
  - Tried doxepin (25mg) - helped with itching
  - Lesions persist daily
  - Failed class II steroid creams, ammonium lactate, aveeno with 0.05% menthol, emollients

Case IV: History (3)

- 8/06: **new symptoms along with hives**
  - Daily Fevers to 100.3 lasting 3 hours
    - Treated with acetaminophen (Tylenol)
  - Night sweats, Bone pain
  - Weight loss (10lbs over 2 mo)
  - Breasts swollen and tender
- 12/06: continued bone pain, fevers, lymphadenopathy, urticaria

Past Medical History

- CAD s/p angioplasty 2000, 2 vessel bypass in 2006 - post-op atrial fib on warfarin (Coumadin)
- HTN - dxed 1990
- Hypercholesterolemia
- Gynecomastia
- GERD
- Family History: no hives/swelling; daughter with non-Hodgkins lymphoma now in remission

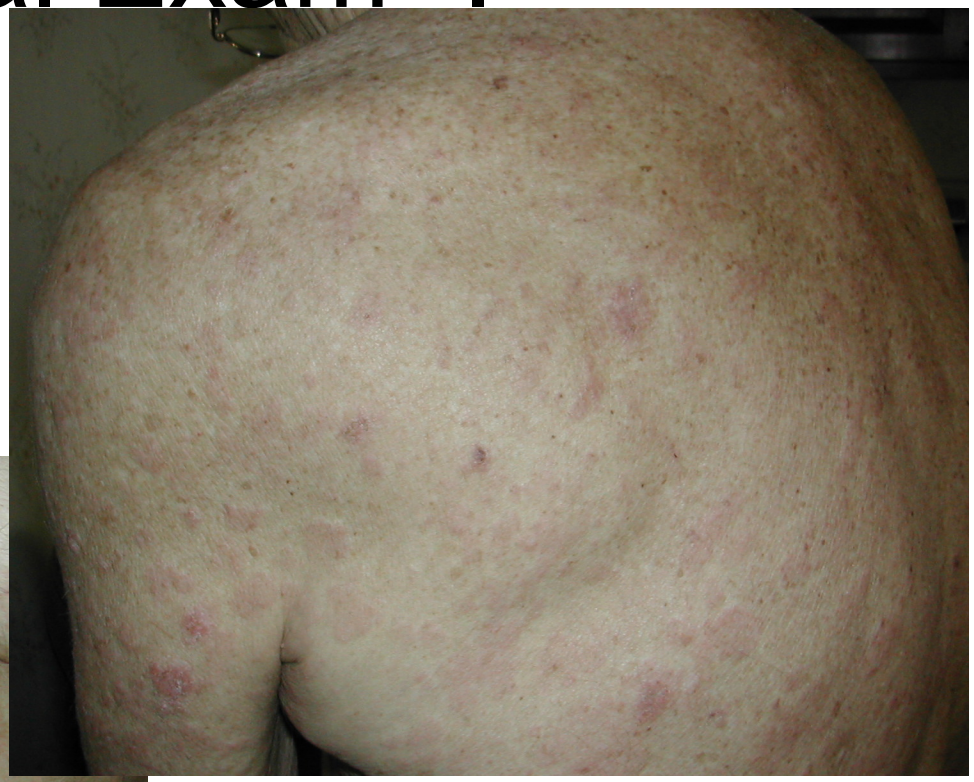
Case IV: Physical Exam

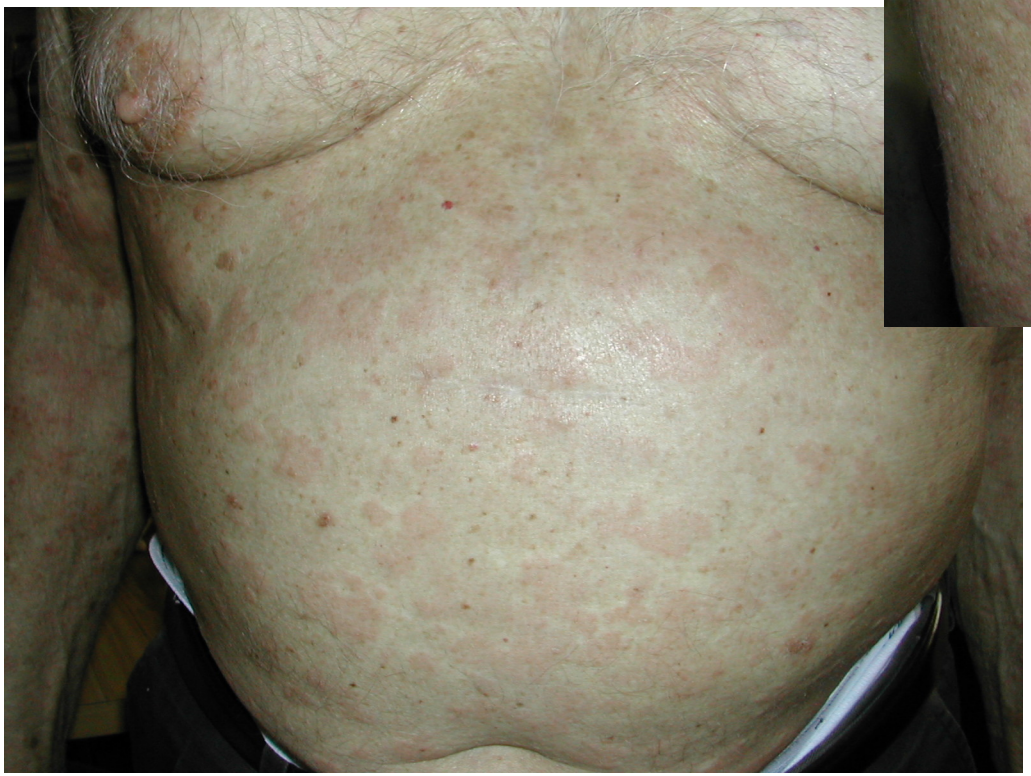
- T 98.4, HR 60, RR 18, BP104/60, Wt 171lbs, Ht 5ft 8
- Gen: thin
- HEENT: sclera nonicteric; bilateral hearing aids; TMs and OP nml; neck supple w/out LAD or thyromegaly
- Lungs: clear
- Chest: Gynecomastia
- CV: irregular rate and rhythm
- Abdomen: soft, NT/ND, no HSM

Physical Exam-II

- Lymph Nodes: 1 cm mobile soft NT node in right axilla and left axilla; multiple 1-2 cm bilateral inguinal nodes (significant change from previous exams)
- Skin: diffuse raised erythematous oval shaped lesions covering almost entire body surface, sparing palms, soles, and face
- Extremities: trace ankle edema bilaterally

Physical Exam -I





Serial CBC's

Date	WBC	Hgb	Hct	Plts	%Lymp	%Mono	%Gran	% Eos	% Bas
7/12/06	9.5	12.5	38.6	185	12.2	5.4	78.7	3.3	0.4
8/14/06	22.2	10.4	33.1	522	6.5	2.6	89.2	1.2	0.1
9/12/06	19.2	10.6	31.6	431	5.9	3.2	90.9		
10/19/06	19.0	10.6	31.2	423	5.1	2.1	92.8		
12/11/06	17.7	10.5	35.0	418	7.8	3.3	85.9	2.5	0.2
3/29/07									
4/12/07									
5/1/07									
5/15/07									

Past laboratory studies

- CRP 8.3 mg/L (nml < 1.0)
- ESR 53 mm/hr (nml 1-20)
- Hepatitis B and C and brucella serologies negative
- C3 and C4 nml
- T4 1.2 ng/dL (0.7-1.6); TSH 4.85 mIU/L (0.4-5.0)
- LH 4.3 mIU/mL (1-10.2) , FSH 5.7 mIU/mL (1.4-14.4), prolactin 5.4 ng/mL (0-18)
- **IgG 1760 mg/dL (694-1618)**
- **IgM 304 mg/dL (48-271)**
- IgA 127 mg/dL (81-463)

Recent Bone Marrow

- Bone marrow biopsy
  - Mildly hypercellular marrow with maturing trilineage hematopoiesis and granulocytic hyperplasia
    - 51% neutrophils (25-40)
    - 5% eosinophils (1-3)
    - 2% lymphocytes (10-15)
  - No evidence of lymphoproliferative disorder
    - Flow cytometry and cytogenetics within NML limits
  - Normal skeletal survey-no lytic lesions
  - Chest/Abd/Pelvis CT-scattered small lymph nodes

New Lab Evaluation

- UPEP: nml pattern with protein excretion within nml limits
- SPEP: total protein 7.7g/dL (6-8.2)
  - Gamma globulin fraction 1.9 g/dL (0.7-1.7)
  - Spike (0.39g/dL) c/w monoclonal protein
  - **Immunofixation positive for IgM kappa monoclonal gammopathy and polyclonal IgG hypergammaglobulinemia**
- **IgG 2030mg/dL (751-1560)**
- **IgM 397mg/dL (36-304)**
- IgA 158mg/dL (82-453)

Case IV- New Imaging

- Chest CT: bilateral axillary LAD, gynecomastia unchanged from 8/06
- Abd/Pelvis CT: inguinal LAD increased from 8/06: largest node 2.6 X 1.7 cm on right, 2.9 X 1.7 cm on left
- Inguinal LN biopsy (1/07):
  - Reactive follicular and interfollicular lymphoid hyperplasia

Diagnosis: Schnitzler's Syndrome

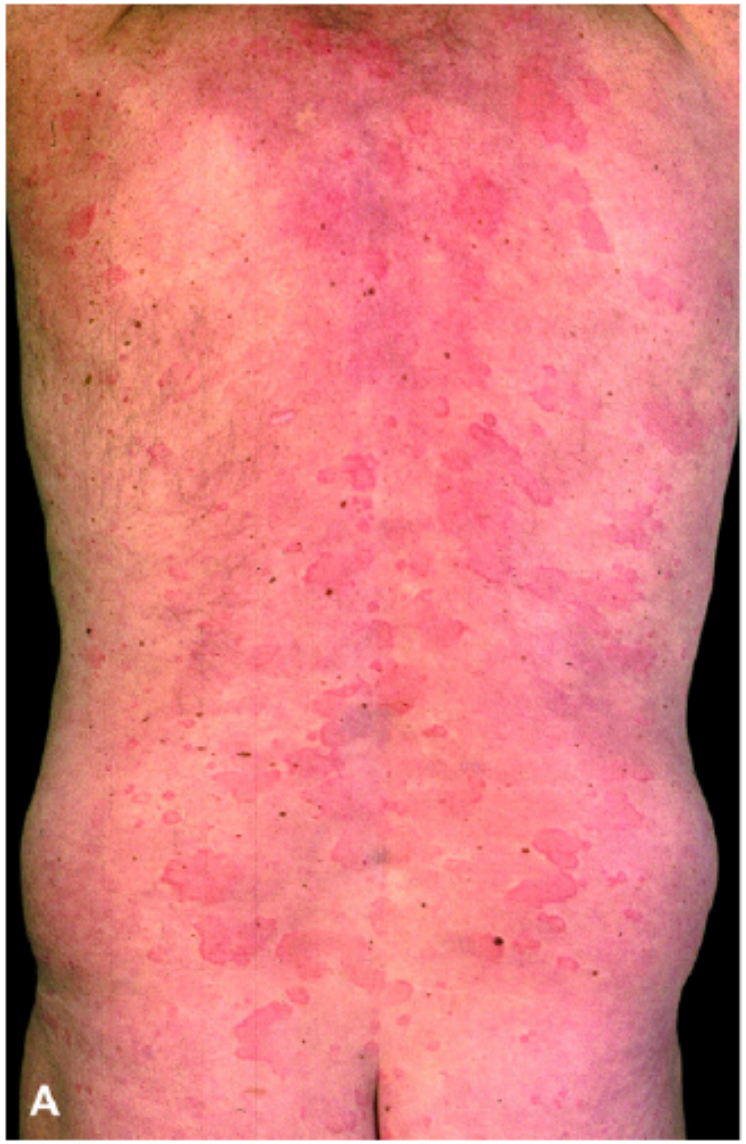
- First reported by French dermatologist in 1972
- Age of onset: 29-79 yrs (mean 60yrs)
- Slight male prevalence (M/F ratio 1.45)
- **Fever, urticaria, IgM monoclonal gammopathy**
- Rare: 50 cases in literature

Schnitzler L Ann Dermatol Venereol 1989; 80:37
Lipsker D Medicine 2001; 80:37

Lipsker D Medicine 2001; 80:37
Almerigogna MG JEADV 2002; 16:214

Urticaria

- Present in 100% of cases
- Lesions: erythematous maculopapular annular lesions
- Usually nonpruritic but 29% of patients report pruritus after 3 or 4 yrs
- Appear simultaneously with fever
- Angioedema very rare
- Histopathogical findings: variable but neutrophilic urticaria most common



Pathogenesis of Urticarial Lesions

- Monoclonal IgM deposits in skin along BM membrane or capillary walls in 25% of patients
- Anti-skin IgM autoAb in serum of patients that recognize epidermal Ags; same isotype as circulating monoclonal Igs
- BUT severity of urticaria not related to level of paraprotein and not all patients show positive staining for IgM in skin

Lipsker D Medicine 2001; 80:37
Lipsker D Br J Dermatol 2000; 142:954

Fever

- Present in 90% of patients
- Usually intermittent with peaks > 40ºC
- Usually well tolerated
- Often accompanied by chills, night sweats

Lipsker D Medicine 2001; 80:37

Monoclonal IgM Component

- Associated with kappa light chain in 89% of patients
- At time of dx: BM examination is normal in 80% of patients; 20% show an unspecific polyclonal lymphocytic or plasmocytic infiltrate

Lipsker D Medicine 2001; 80:37

Musculoskeletal Involvement

- Bone pain present in 70% of patients
  - Most common: iliac bone and tibia
- Arthralgia/arthritis in 59% of patients
- Radiographic findings: osteosclerosis involving mainly cortices of long bones
  - Lytic lesions rare
- No reports of joint destruction or deformities

Lipsker D Medicine 2001; 80:37
Almerigogna MG JEADV 2002; 16:214

Lymphadenopathy and Hepatosplenomegaly

- LAD in 40% of patients
  - Axillary and inguinal LN most common
- Hepatomegaly in 30% of patients
- Splenomegaly less common

Lipsker D Medicine 2001; 80:37
Almerigogna MG JEADV 2002; 16:214

Therapy of Schnitzler's

- Koning et al reported complete remission in 3 patients with Schnitzler's treated with Anakinra
  - Anti-IL-1 receptor antagonist, used in RA
  - Treatment: 100 mg SC daily
  - Fever/skin lesions resolved within 24hrs
  - All patient still in remission after 6-18 mo
  - SE's infection risks,injection site discomfort
- 2 other case reports demonstrating success in patients with refractory Schnitzlers

Martinez-Taboada VM Arthritis Rheum 2005; 52(7):2226
Schneider J Am Acad Dermatol 2007; 56(5):S120
de Koning HD Ann Rheum Dis 2006; 65:542

Prognosis

- Benign course in 85% of patients
- Some patients may go on to develop lymphoproliferative disorder
  - Usually Waldenstrom dz or lymphoma
  - No specific predictive factor for development of lymphoproliferative dz
  - Long-term f/up is needed
    - SPEP/UPEP and Ig subtype levels biannually
    - LN bx when enlargement noted

Lipsker D Medicine 2001; 80:37
Almerigogna MG JEADV 2002; 16:214

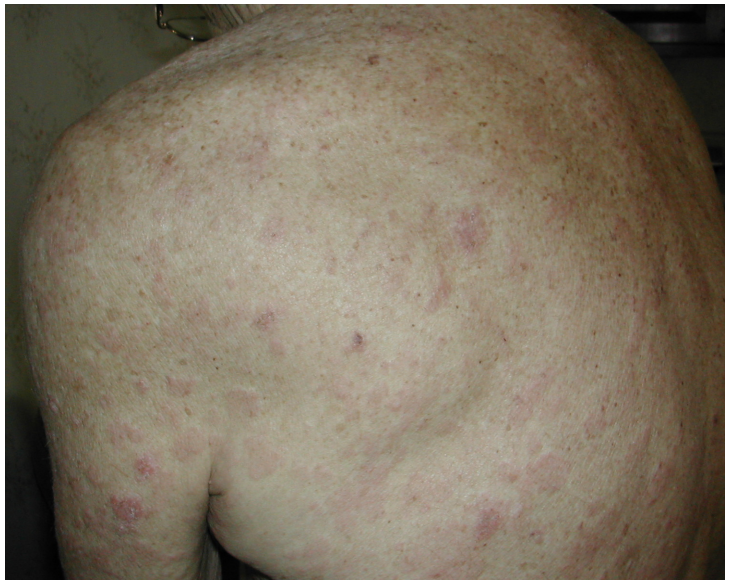
Case IV- Clinical course

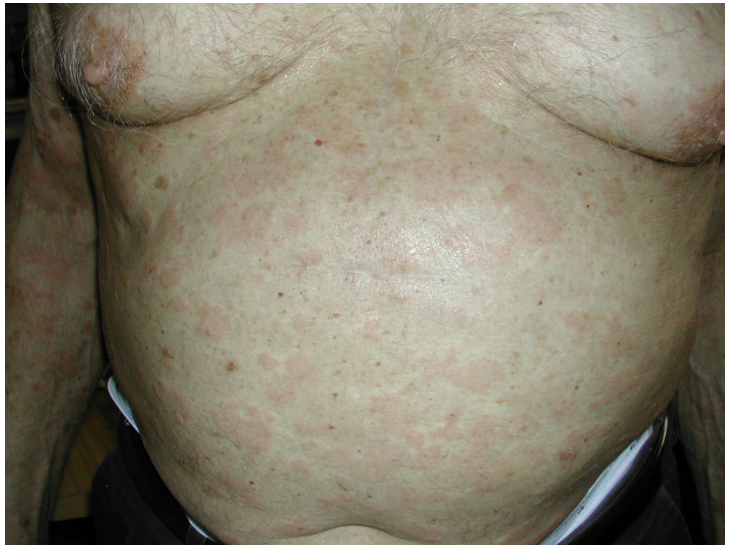
- 2/07: started on 1 mo prednisone taper (max. dose 20 mg/day)
  - Cough and fevers resolved
  - Rash improved by 40-50% (no change in pruritus)
  - All sxs returned to pre-tx severity once weaned to 5mg/day

Clinical course II

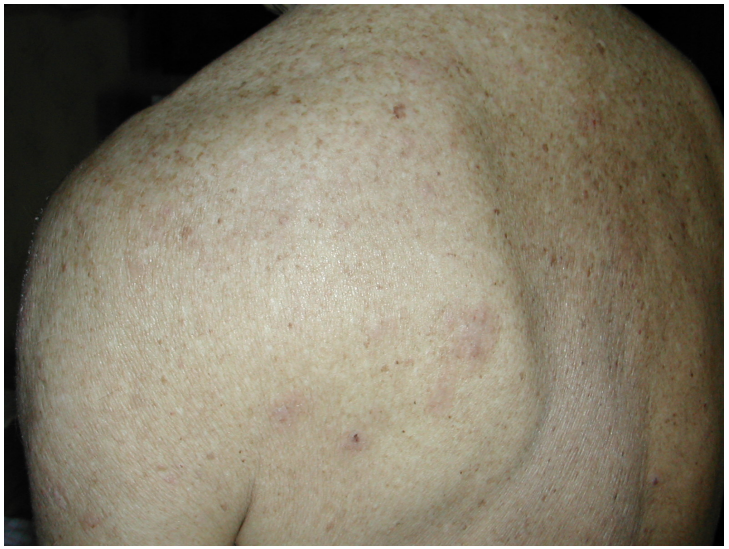
- 3/07: started on kineret (100mg/day SC)
  - Within days: rash gone
  - Cough resolved after 1 weeks
  - LAD improved over weeks

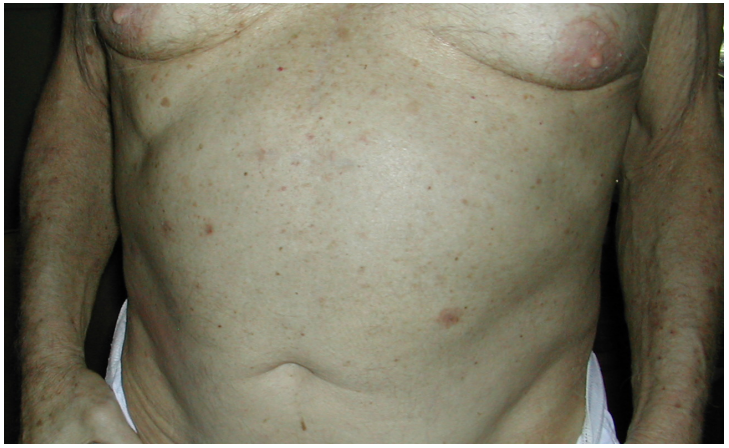
Before





After

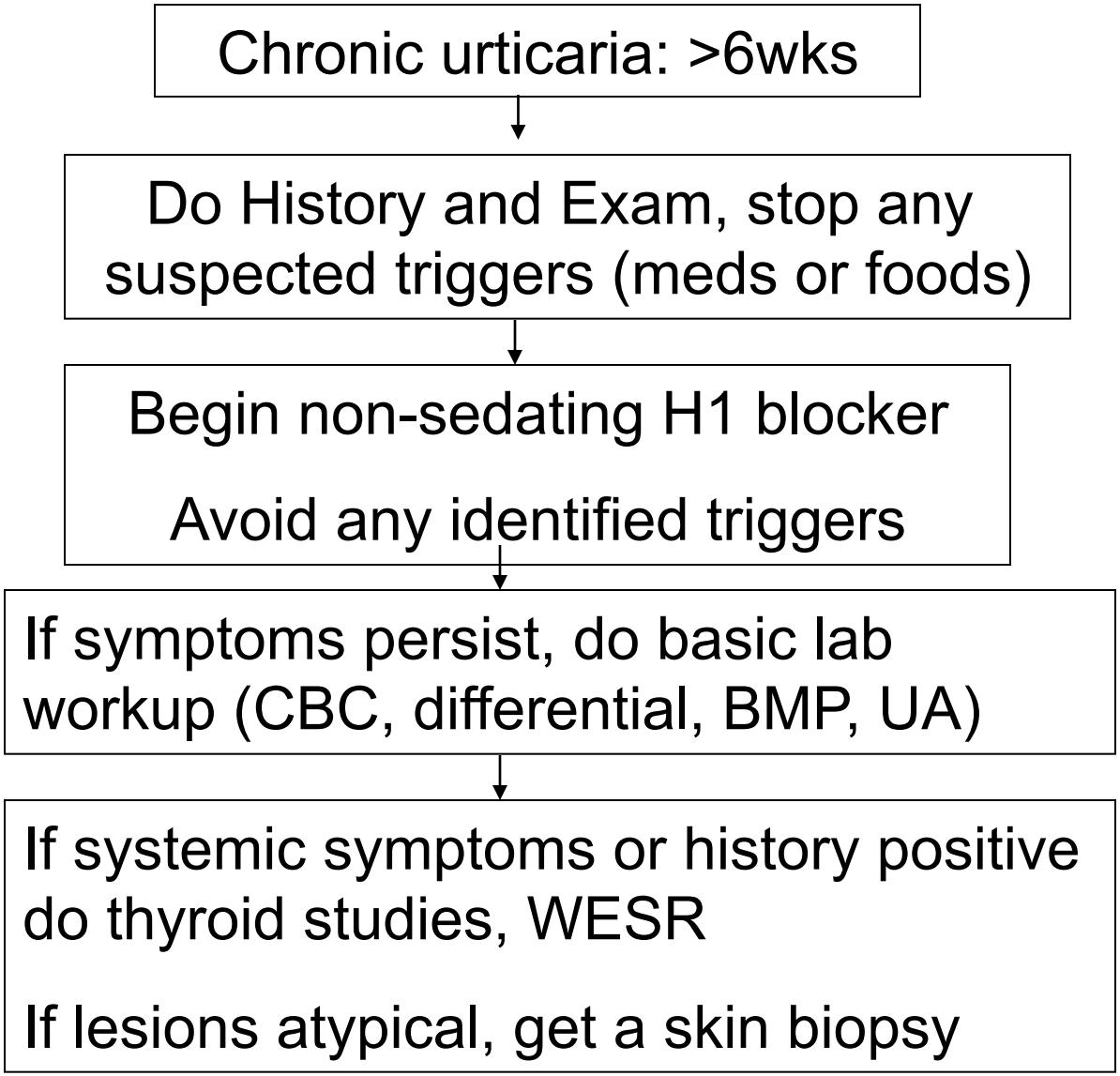




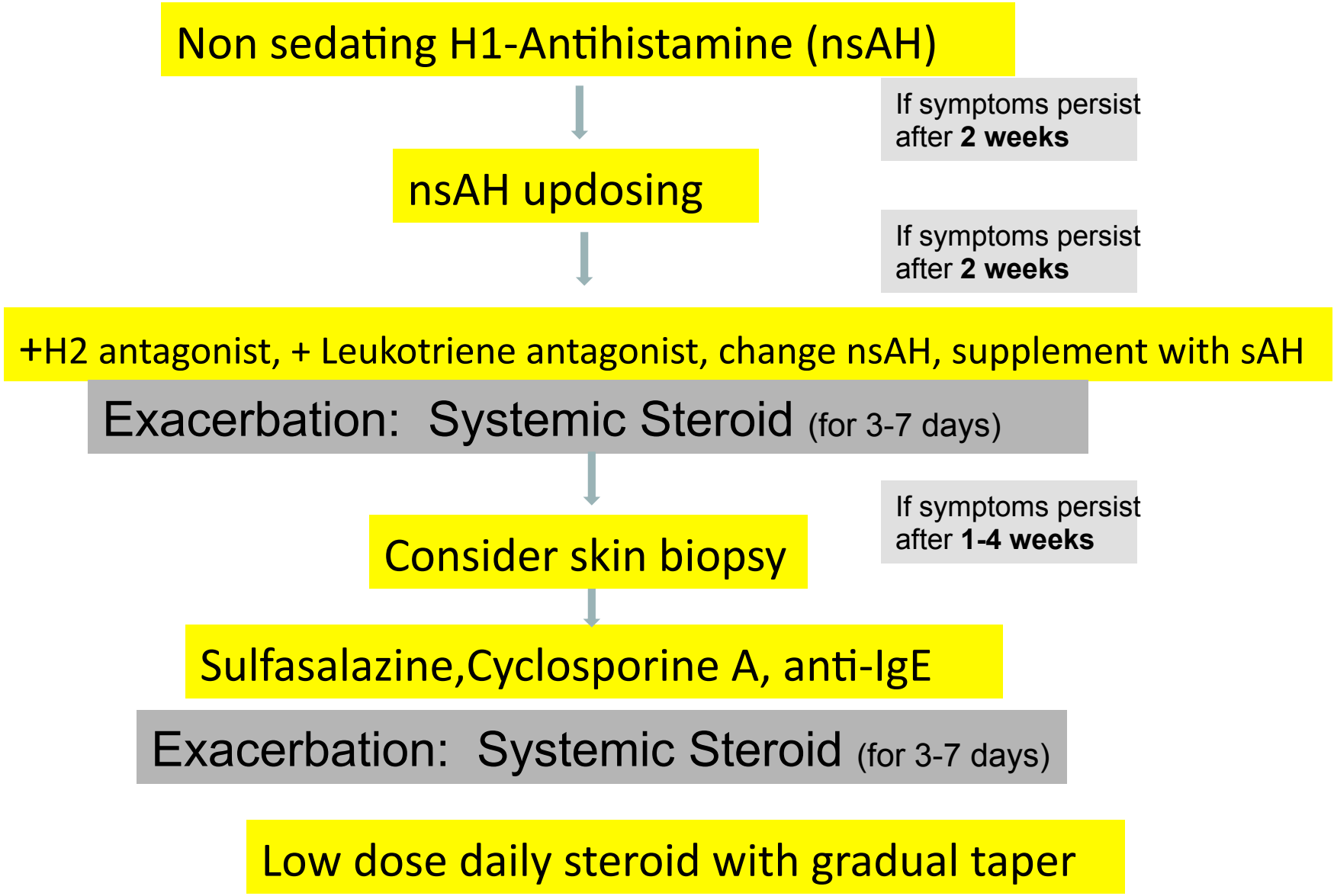
Date	WBC	Hgb	Hct	Plts	%Lymp	%Mono	%Gran	% Eos	% Bas
7/12/06	9.5	12.5	38.6	185	12.2	5.4	78.7	3.3	0.4
8/14/06	22.2	10.4	33.1	522	6.5	2.6	89.2	1.2	0.1
9/12/06	19.2	10.6	31.6	431	5.9	3.2	90.9		
10/19/06	19.0	10.6	31.2	423	5.1	2.1	92.8		
12/11/06	17.7	10.5	35.0	418	7.8	3.3	85.9	2.5	0.2
3/29/07	6.4	12.5	38.6	185					
4/12/07									
5/1/07									
5/15/07									

Summary

- Schnitzler's syndrome is characterized by chronic urticarial rash, monoclonal IgM gammopathy, fevers, bone pain, and elevated inflammatory markers
- Etiology unknown
- Anakinra (Kineret) may be an effective tx strategy in refractory cases



Adapted from Amr and Dreskin, 2008



Modified from Urticaria Guidelines- October 2009 *Allergy*